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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/557,586	03/03/2006	Maria Assunta Costa	1136-PCT-US	8745

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EXAMINER	
ROONEY, NORA MAUREEN	
ART UNIT	PAPER NUMBER
1644	
MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/557,586	COSTA ET AL.	
	Examiner	Art Unit	
	NORA M. ROONEY	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 April 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-13* is/are pending in the application.

4a) Of the above claim(s) *8-10* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7 and 11-13* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *17 November 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *11/17/2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's election with traverse of Group I, claims 1-7 and 11-13 in the reply filed on 04/17/2008 is acknowledged. The traversal is on the ground(s) that Applicants submit that claims 1-13, Inventions 1 and 2, do not require restriction as they are connected by a single technical relationship, which is a multimer protein comprising at least a first amino acid sequence having substantially the sequence of *one* of the *Parietaria judaica* major allergens Par j 1 or Par j 2 and a second amino acid sequence having substantially the sequence of one of the *Parietiria judaica* major allergens Par j 1 or Par j2. This is not found persuasive because as set forth in the restriction requirement mailed on 03/20/2008, the claims lack a special technical feature over Vrtala et al. in view of Colombo et al.

The requirement is still deemed proper and is therefore made FINAL.

2. Claims 8-10 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected Group, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 04/17/2008.

3. Claims 1-7 and 11-13 are currently under examination as they read on a multimer protein molecule comprising at least a first amino acid sequence having substantially the sequence of one of the *Paraietaria judaica* major allergens Par j 1 or Par j 2 and a second amino acid sequence having substantially the sequence of one of the *Parientaria judaica* major allergens Par j 1 or Par j 2 and a pharmaceutical composition comprising said multimer protein.

4. Applicant's IDS document filed on 11/17/2005 is acknowledged.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 1-7 and 11-13 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. The term "substantially the sequence" in claims 1, 3, 5,-7 and "substantially comprising" in claim 4 are relative terms which render the claims indefinite. The terms "substantially the sequence" and "substantially comprising" are not defined by the claims and the specification does not provide a standard for ascertaining the degree of amino acid identity contemplated.

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 1-7 and 11-13 *are* rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for: a multimer protein comprising a plurality of proteins selected from the group consisting of SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3 and SEQ ID NO:4 , does not provide reasonable enablement for: a multimer protein molecule comprising at

least a first amino acid sequence **having substantially the sequence of one of the *Parietaria judaica* major allergens Par j 1 or Par j 2** and a second amino acid sequence **having substantially the sequence of one of the *Parietiria judaica* major allergens Par j 1 or Par j 2** of claim 1; further comprising at least a 'third sequence of **one of the *Parietaria judaica* major allergens Par j 1 or Par j 2 of claim 2**; wherein the sequence of the major allergen Par j 1 is **substantially the sequence Seq Id No. 1** and the sequence of the major allergen Par j 2 is **substantially the sequence Seq Id No. 3** of claim 3; wherein the sequence of the *Parietaria judaica* major allergen Par j 1 and/or of the major allergen Par j 2 **is mutated in the loop 1 amino acid region, substantially comprising from amino acid 1 to 30 of Seq Id No. 1 and/or of Seq Id No. 3** of claim 4; wherein the mutated sequence of the major allergen Par j 1 **is substantially the sequence Seq Id No. 2** of claim 5; wherein the mutated sequence of the major allergen Par j 2 **is substantially the sequence Seq Id No. 4** of claim 5; wherein the mutated sequence of the major allergen Par j 1 **is substantially the sequence Seq Id No. 2** and **the** mutated sequence of the major allergen Par j 2 is **substantially the sequence Seq Id No. 4** of claim 7; the multimer protein molecule according to claim 1 **for medical use** of claim 11; The multimer protein molecule according to claim 1 **for medical use as a hypoallergenic agent** of claim 12; and a **pharmaceutical composition** comprising an effective and acceptable amount of the multimer protein molecule according to claim 1 and suitable adjuvants and/or diluents of claim 13. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and or use the invention commensurate in scope with this claim.

The specification disclosure does not enable one skilled in the art to practice the invention without an undue amount of experimentation.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention.

The specification discloses the generation of a multimer protein comprising a plurality of proteins selected from the group consisting of SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3 and SEQ ID NO:4.

The specification does not adequately disclose a multimer protein comprising proteins that are "substantially the sequence" of a protein selected from the group consisting of SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3 or SEQ ID NO:4. The term "substantially the sequence" gives no specific indication of what proteins are encompassed by the instant claim recitation. As recited, proteins that are "substantially the sequence of" any regions of SEQ ID NO:s 1-4 are encompassed. It would require undue experimentation by one of ordinary skill in the art to make and use proteins that are "substantially the sequence of" the recited proteins because the specification offers no guidance or examples on what qualifies as a protein that is substantially

the sequence of SEQ ID NOs 1-4 and what regions of the proteins of SEQ ID NOs 1-4 are important and must be retained in order to qualify as being "substantially the sequence of."

The specification does not adequately disclose a method of detecting the presence of a multimer protein comprising proteins that are "substantially comprising from amino acid 1 to 30 of SEQ ID NO:1 and/or of SEQ ID NO:3"of claim 4. The term " substantially comprising from amino acid 1 to 30" gives no specific indication of what proteins are encompassed by the instant claim recitation. As recited, proteins that are comprising any of amino acid 1 to 30 of SEQ iD NOs 3 or 4 are encompassed. It would require undue experimentation by one of ordinary skill in the art to make and use proteins that are " substantially comprising from amino acid 1 to 30 of SEQ ID NO:1 and/or of SEQ ID NO:3" because the specification offers no guidance or examples on what qualifies as a substantially comprising and what regions of the proteins are important and must be retained in order to qualify as being " substantially comprising from amino acid 1 to 30 of SEQ ID NO:1 and/or of SEQ ID NO:3."

The specification has not adequately disclosed any Par j 1 or Par j 2 allergen mutant that has been mutated at any amino acid in the area corresponding to loop 1 (amino acids 1 to 30 of SEQ ID NOs 1 or 3) for use in the claimed invention. The specification has only disclosed the mutants of SEQ ID NOs 2 and 4 for use in the claimed invention. Without guidance in the specification as to what areas to avoid making mutation and/or guidance regarding how to make mutations in designated areas, the resulting mutated polypeptides will have unpredictable activities and binding properties. The art of Blumenthal et al. teaches that a determination of IgE

antibody binding to proteins cannot be made a priori based upon antigen structure (PTO-892, Reference U, whole document and page 39 of third full paragraph). Further, mutating certain amino acids may abolish antibody binding altogether as in the case of Colman et al. (PTO-892, Reference V, whole document) and Abaza et al. (PTO-892, Reference W, whole document), or could increase antibody binding as in the case of Maleki et al. (PTO-892; Reference W, whole document) which teaches that the denaturation of allergenic proteins (often the result of alteration of disulfide bridges) can increase IgE binding. In either case, the resulting mutants are likely to not be useful in the claimed invention directed to multimers which have therapeutic and diagnostic purpose.

Also at issue is whether or not the multimer proteins disclosed will have medicinal and/or pharmaceutical use. In view of the absence of a specific and detailed description in Applicant's specification of how to effectively use the protein as a medicament or pharmaceutical composition as claimed, absence of working examples providing evidence which is reasonably predictive that the claimed composition is effective for in vivo use to treat allergy, and the lack of predictability in the art at the time the invention was made, an undue amount of experimentation would be required to practice the claimed pharmaceutical composition with a reasonable expectation of success.

Substantiating evidence may be in the form of animal tests, which constitute recognized screening procedures with clear relevance to efficacy in humans. See Ex parte Krepelka, 231 USPQ 746 (Board of Patent Appeals and Interferences 1986) and cases cited therein. Ex parte

Maas, 9 USPQ2d 1746.

Reasonable correlation must exist between the scope of the claims and scope of the enablement set forth. In view on the quantity of experimentation necessary the limited working examples, the nature of the invention, the state of the prior art, the unpredictability of the art and the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

9. Claims 1-7 and 11-13 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant is in possession of: a multimer protein comprising a plurality of proteins selected from the group consisting of SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3 and SEQ ID NO:4.

Applicant is not in possession of: a multimer protein molecule comprising at least a first amino acid sequence **having substantially the sequence of one of the *Parietaria judaica* major allergens Par j 1 or Par j 2** and a second amino acid sequence **having substantially the sequence of one of the *Parietiria judaica* major allergens Par j 1 or Par j 2** of claim 1; further comprising at least a 'third sequence of **one of the *Parietaria judaica* major allergens Par j 1 or Par j 2 of claim 2**; wherein the sequence of the major allergen Par j 1 is **substantially the sequence Seq Id No. 1** and the sequence of the major allergen Par j 2 is **substantially the sequence Seq Id No. 3** of claim 3; wherein the sequence of the *Parietaria judaica* major

allergen Par j 1 and/or of the major allergen Par j 2 **is mutated in the loop 1 amino acid region, substantially comprising from amino acid 1 to 30 of Seq Id No. 1 and/or of Seq Id No. 3** of claim 4; wherein the mutated sequence of the major allergen Par j 1 **is substantially the sequence Seq Id No. 2** of claim 5; wherein the mutated sequence of the major allergen Par j 2 **is substantially the sequence Seq Id No. 4** of claim 5; wherein the mutated sequence of the major allergen Par j 1 **is substantially the sequence Seq Id No. 2** and **the** mutated sequence of the major allergen Par j 2 is **substantially the sequence Seq Id No. 4** of claim 7.

Applicant has disclosed only a multimer protein comprising a plurality of proteins selected from the group consisting of SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3 and SEQ ID NO:4; therefore, the skilled artisan cannot envision all the contemplated multimer protein possibilities recited in the instant claims. Consequently, conception cannot be achieved until a representative description of the structural and functional properties of the claimed invention has occurred, regardless of the complexity or simplicity of the method.

Adequate written description requires more than a mere statement that it is part of the invention. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC1993). The Guidelines for the Examination of Patent Application Under the 35 U.S.C.112, ¶1"Written Description" Requirement make clear that the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species disclosure of relevant, identifying characteristics, i.e., structure or other physical and or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and

structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the genus (Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 20001, see especially page 1106 3rd column).

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the written description inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.). Consequently, Applicant was not in possession of the instant claimed invention. See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.

Applicant is directed to the final Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Claim Rejections - 35 USC § 103

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

11. Claims 1-7 and 11-13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Vrtala et al. (Reference 10; IDS filed on 11/17/2005) in view of Colombo (Reference 7; IDS filed on 11/17/2005).

Vrtala et al. teaches recombinant multimeric protein allergen such as dimer and trimer of major birch pollen allergen Bet vl, (In particular, page 2045 and whole document). The recombinant trimer consisting of three covalently linked copies of the allergens is useful for inducing IgG antibodies in vivo (pharmaceutical composition, for medical use as a hypoallergenic agent, comprising diluents) and blocking IgE binding to Bet vl and related allergens, (In particular, abstract and page 2047).

The claimed invention differs from the prior art in the recitation of "comprising at least a first amino acid sequence having substantially the sequence of one of the *Parietaria judaica* major allergens Par j 1 or Par j 2 and a second amino acid sequence having substantially the sequence of one of the *Parietiria judaica* major allergens Par j 1 or Par j 2" of claim 1; "further comprising at least a 'third sequence of one of the *Parietaria judaica* major allergens Par j 1 or Par j 2" of claim 2; "wherein the sequence of the major allergen Par j 1 is substantially the sequence Seq Id No. 1 and the sequence of the major allergen Par j 2 is substantially the sequence Seq Id No. 3" of claim 3; "wherein the sequence of the *Parietaria judaica* major allergen Par j 1 and/or of the major allergen Par j 2 is mutated in the loop 1 amino acid region, substantially comprising from amino acid 1 to 30 of Seq Id No. 1 and/or of Seq Id No. 3" of claim 4; "wherein the mutated sequence of the major allergen Par j 1 is substantially the sequence Seq Id No. 2" of claim 5; "wherein the mutated sequence of the major allergen Par j 2 is substantially the sequence Seq Id No. 4" of claim 5; and "wherein the mutated sequence of the

major allergen Par j 1 is substantially the sequence Seq Id No. 2 and the mutated sequence of the major allergen Par j 2 is substantially the sequence Seq Id No. 4" of claim 7.

Colombo et al teaches Par j 1 and Par j2 allergens (having substantially the same sequences as SEQ ID NO:1 and 3) and loop 1 allergen mutants mutated in amino acids 1-30 (having substantially the same sequences as SEQ ID NO:2 and 4) for diagnosis and therapy of pollen allergy (In particular, pages 199-200 'Materials and Methods', sequences in Table 2, whole document).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the Par j 1 and Par j2 allergens taught by Colombo in the major birch pollen allergen Bet vl dimers and trimers of Vrtala et al because Vrtala et al. teaches that the dimers and trimers are useful for diagnosis and/or treating allergy. Colombo et al. teaches that Par j1 and Pa j 2 can themselves be useful for diagnosis and therapy of Parietaria pollen allergy, so it would be obvious to generated multimers of the allergens for diagnosis and therapy as well.

From the reference teachings, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the reference, especially in the absence of evidence to the contrary.

12. No claim is allowed.

13. Any inquiry concerning this communication or earlier communications from the

examiner should be directed to Nora M. Rooney whose telephone number is (571) 272-9937. The examiner can normally be reached Monday through Friday from 8:30 am to 5:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Eileen O'Hara can be reached on (571) 272-0878. The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

September 2, 2008
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Art Unit 1644